Is ambient temperature associated with risk of infant mortality? A multi-city study in Korea

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ARTICLE INFO

ABSTRACT

Background: Although numerous studies have shown increased risk of mortality from elevated temperatures for adults, limited studies have examined temperature's effect on mortality for infants. Our study investigated the city-specific and overall effects of ambient temperature on infant mortality in seven major cities in Korea, 2004–2007.
Methods: Birth cohort using a linked birth and death records included 777,570 births with 557 all-cause deaths. We estimated city-specific hazard ratios for each city using an extended Cox proportional hazards model with time-dependent covariates. Then we combined city-specific hazard ratios to generate overall hazard ratio across the seven cities using a Bayesian hierarchical model. Stratified analyses were conducted by cause of death (total and SIDS), exposure period (whole gestation, each trimester, lifetime, 1 month before death, and 2 weeks before death), sex, and maternal characteristics.
Results: Overall across the cities, we found significantly positive associations between ambient temperature during 1 month before death or 2 weeks before death and infant mortality from total or SIDS. The overall hazard ratio of infant mortality from total deaths and SIDS for a 1 °C increase during 1 month before death was 1.52 (95% CI, 1.46–1.57) and 1.50 (95% CI, 1.35–1.66), respectively. We also found suggestive evidence that some factors such as mother's age may modify the association.
Conclusions: Our findings have implications for establishment of policy to reduce the risk of infant mortality from high ambient temperature under climate change.

1. Introduction

Numerous studies conducted in many parts of the world have demonstrated associations between ambient temperature and mortality (Goggins et al., 2015; Vardoulakis et al., 2014; Wang et al., 2015; Yang et al., 2015). Moreover, significantly raised risks of heat- and cold-related mortality are anticipated under climate change (Hajat et al., 2014). Given that climate change is expected to result in more severe weather patterns with overall warming in the future, it is important to investigate the impacts of temperature on health outcomes and establish appropriate strategies for potential high risk populations.

Previous studies reported variability in vulnerability to temperature-related health effects by sub-population. People with low socioeconomic status, the elderly, and children are often reported to be at greater risk from high ambient temperature (Basu and Malig, 2011; Basu and Ostro, 2008; Basu and Samet, 2002a). Baccini et al. (2008) reported stronger associations between heat and mortality in the elderly (≥ 75) than other age groups. Other studies investigating temperature

and mortality also suggest that the elderly are particularly vulnerable (Hajat et al., 2007; Medina-Ramón et al., 2006; Stafoggia et al., 2006). Another study reported that very young children, especially infants, are particularly vulnerable to heat-related deaths (Xu et al., 2012). Although a few studies reported that infants are more susceptible to heat-related mortality (Basagaña et al., 2011; Basu et al., 2015; Basu and Ostro, 2008), most studies focused on the general population or the elderly and limited studies exist for temperature's mortality effect on infants.

Possible biological mechanisms of heat exposure with mortality include decreased blood circulation to the heart and vital organs resulting from changes in blood composition such as increased platelet and red blood cell counts, blood viscosity, and plasma cholesterol levels due to heat stress (Bouchama and Knochel, 2002; Keatinge et al., 1986). In particular, infants' vulnerability to high temperature may be related to thermal instability. Infants may be especially vulnerable to heat due to several physiologic differences such as increased ratio of body surface area to body mass and metabolic rate, higher sweating threshold,

smaller blood volume and their immaturity of thermoregulatory mechanisms, and lack of self-care ability from heat stress (Basagaña et al., 2011; Guntheroth and Spiers, 2001; Xu et al., 2012).

Of the few studies that investigated temperature and mortality for infants, most focused on a single city. Temperature effects may differ by area because of different regional characteristics such as climatic characteristics, use of air conditioning, and individual behaviors (e.g., spend time outdoors) or other characteristics. Thus, more studies in various locations and study populations are needed.

We investigated the city-specific and overall effects of ambient temperature on infant mortality in seven major cities in Korea. We considered several timeframes of heat exposure on infant mortality and effect modification by infant sex and mother's age and education.

2. Material and methods

2.1. Data

We obtained linked birth and death records for 2004–2007 from the Korean National Statistical Office for seven major cities in Korea (Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, and Ulsan). Linked data included residential address, sex, birth weight, gestational age, birth order, date of birth, mother's age, mother's education, date of death, age at death, and cause of death. We excluded subjects with incomplete data for covariates for infant's sex, gestational age, birth weight, and maternal characteristics (i.e., mother's age or education). We restricted study subjects to singleton births with 37–44 weeks of gestation. Also, we excluded infants who died prior to the postneonatal period (i.e., those who died in the first 27 days after birth) to consider only deaths more plausibly related with exposure of our interest because death before the postneonatal period tended to occur from pregnancy complications (Woodruff et al., 2006). The study includes 777,570 births with 557 all-cause deaths. We considered total mortality as all causes of death except external causes (International Classification of Diseases, ICD-10, A00-R99), and sudden infant death syndrome (SIDS; ICD-10, R95).

Hourly measurements of ambient temperature for each city were obtained from the National Meteorological Administration, Republic of Korea. We calculated 24-hr average values for each city. We considered long-term exposures for ambient temperature for each study subject for: (1) gestational exposure from conception to birth, (2) exposure for each trimester, (3) lifetime exposure from birth to death or end of eligibility for outcome (1 year of age), (4) 1 month before death, and (5) 2 weeks before death. Trimesters were defined as 1–13 weeks, 14–26 weeks, and 27 weeks to birth. As a sensitivity analysis, we performed analysis with and without air pollution exposure adjustment. We obtained hourly PM_{10} concentration for each city for the study period from the Department of Environment, Republic of Korea. $PM_{2.5}$ data were not available. We calculated daily values (i.e., 24-hr averages) for each city and considered exposures for the gestation period, each trimester, lifetime and 1 month or 2 weeks before death.

2.2. Statistical analysis

At the first stage, we estimated city-specific hazard ratios for each city. We applied an extended Cox proportional hazards model with time-dependent covariates to estimate the association between long-term exposure to ambient temperature and infant mortality. This model assumes that the effect of a time-dependent variable $X_i(t)$ (in this case ambient temperature) on the hazard at time t depends on the values of this variable at that same time t, and not on the value at an earlier or later time. This approach allowed us to examine the effects relative to other subjects for the same follow-up interval. This is similar to the matching used in other studies to compare the exposure levels between the deceased and surviving subjects until the time of death (Woodruff et al., 2006). We analyzed separate models for each cause of death

(total and SIDS) and exposure period (whole gestation, each trimester, lifetime, 1 month before death, and 2 weeks before death). For each cause of death and exposure period, we fitted a time-dependent Cox proportional hazards model:

$$h_i(t) = h_0(t) \exp\left[\beta_1 X_i + \beta_2 X_i(t)\right] \tag{1}$$

where $h_0(t)$ is the unspecified baseline hazard function, X_i is the vector of time-independent variables (sex, birth weight, gestational age, mother's age, mother's educational level, and season of birth) for subject i, $X_i(t)$ is the vector of the time-dependent variable (temperature), and β_j ($j = 1, 2$) are vectors of model parameters. We categorized mother's age (< 25, 25–30, 30–35, and ≥ 35 years) and mother's education (≤ 12, > 12 years). As a next step, we combined city-specific hazard ratios to generate an overall hazard ratio across the seven cities using a Bayesian hierarchical model that incorporates with-city and between-city variances.

To examine the critical exposure window to heat exposure for infant mortality, first we conducted analysis for Seoul, which has the largest population of any city in Korea. We estimated hazard ratios based on different exposure timeframes (whole gestation, each trimester, lifetime, 1 month before death, and 2 weeks before death) for Seoul. We then estimated city-specific and overall hazard ratios for exposure timeframes for which we observed associations. To estimate heat exposure, many environmental health studies have used several measures to consider combined exposure of several weather conditions such as heat index. Thus, we performed sensitivity analysis using a heat index which is a function of air temperature and relative humidity instead of ambient temperature for Seoul. We used a heat index algorithm by the U.S. National Weather Service (NWS) (NWS, 2016). We estimated hazard ratios of infant mortality for total deaths and SIDS for exposure timeframes for which we observed associations and then compared with original findings using an ambient temperature. We also conducted sensitivity analyses to consider: (1) the long-term time trend and seasonality; and (2) temperature variation for Seoul. We estimated hazard ratios of total infant mortality for exposure timeframes for which we observed associations and then compared results with original findings.

We assessed nonlinear associations between continuous temperature and the hazard of infant mortality via restricted cubic splines. We considered 3 (10th, 50th, and 90th temperature percentiles) and 5 knots (10th, 25th, 50th, 75th and 90th temperature percentiles) for splines. Results of the analysis suggested a linear association between increased temperature and risk of infant mortality. Stratified analyses were conducted by characteristics (i.e., infant's sex, mother's age and education level). All analyses were conducted with SAS (version 9.4; SAS Institute Inc., Cary, NC, USA) and R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Table 1 and Table S1 provide summary statistics of key study variables and distribution of daily ambient temperature for the seven major cities in Korea. The number of all-cause deaths ranged from 34 in Gwangju to 233 in Seoul. Average daily mean temperatures were generally similar across the seven cities, ranging from 12.7 °C in Incheon to 14.8 °C in Ulsan. Most infants for all cities were male and had a mother who was 25–30 or 30–35 years of age at time of birth. Mother's education level for all cities except for Incheon averaged more than 12 years, which ranged from 53.6% to 66.3% for a given city.

Table 2 shows hazard ratios for a 1 °C increase based on various exposure windows in Seoul, Korea. We conducted separate analysis by cause of death and exposure timeframe. We found that heat exposure during 1 month before death or 2 weeks before death was associated with infant mortality. The hazard ratio of infant mortality for total deaths and SIDS for a 1 °C increase during 1 month before death was 1.46 (95% confidence interval (CI), 1.44–1.47) and 1.44 (95% CI,

Table 1

Summary statistics for the birth cohort of seven major cities in Korea, 2004–2007.

City	Eligible births	No. of death (All-cause)	Temperature (°C) [mean ± SD]	Mother's age [years, (%)]				Mother's education [years, (%)]		Male (%)
				< 25	25–30	30–35	≥ 35	≤ 12	> 12	
Seoul	356,399	233	13.0 ± 10.1	4.5	36.3	46.6	12.5	33.5	66.3	51.4
Busan	100,544	78	14.7 ± 8.0	6.5	39.1	43.1	11.3	39.1	60.6	51.4
Incheon	91,384	72	12.7 ± 9.4	8.4	41.0	39.4	11.3	54.2	45.5	51.3
Daegu	80,364	63	14.7 ± 9.3	6.3	41.2	42.4	10.1	35.7	64.1	51.9
Daejeon	55,168	40	13.2 ± 9.7	7.7	41.3	40.7	10.3	35.7	64.0	51.6
Gwangju	52,469	34	14.2 ± 9.3	8.2	42.8	38.7	10.2	35.8	63.9	51.8
Ulsan	41,242	37	14.8 ± 8.5	7.7	43.3	39.6	9.5	46.3	53.6	52.4

Table 2

Hazard ratios for a 1 °C increase based on various exposure metrics in Seoul, Korea, 2004–2007.

Exposure	Total Mortality (N = 233)	SIDS (N = 26)
Whole gestation	0.935 (0.872–1.004)	0.901 (0.727–1.118)
1st trimester	1.000 (0.986–1.015)	0.964 (0.923–1.007)
2nd trimester	0.980 (0.956–1.005)	0.968 (0.897–1.044)
3rd trimester	0.999 (0.985–1.014)	1.035 (0.990–1.083)
Lifetime	0.955 (0.872–1.045)	1.129 (0.816–1.561)
1 month before death	1.457 (1.440–1.474)	1.437 (1.387–1.489)
2 weeks before death	1.461 (1.444–1.479)	1.434 (1.382–1.488)

Adjusted for sex, birth weight, gestational week, mother's age, mother's education level, season of birth.

1.39–1.49), respectively. Hazard ratios for 2 weeks before death were similar with those of 1 month before death (1.46 (95% CI, 1.44–1.48) for total mortality; 1.43 (95% CI, 1.38–1.49) for SIDS). For exposure from gestational, each trimester, and lifetime, we did not find statistically significant associations between temperature and any cause of infant mortality.

For exposure timeframes for which we observed significant associations (i.e., exposure during 1 month before death or 2 weeks before death), we estimated city-specific and overall hazard ratios (Table 3). The hazard ratio of total infant mortality for a 1 °C increase in exposure during 1 month before death was the highest in Busan (1.61, 95% CI:

Table 3

Hazard ratios for a 1 °C increase in each exposure metric from Cox proportional hazards models in a birth cohort, Korea, 2004–2007.

Exposure	Eligible births	Total mortality	N	SIDS	N
1 month before death					
Seoul	356,399	1.457 (1.440–1.474)	233	1.437 (1.387–1.489)	26
Busan	100,544	1.608 (1.563–1.655)	78	1.589 (1.494–1.690)	20
Incheon	91,384	1.486 (1.452–1.521)	72	–	7
Daegu	80,364	1.581 (1.531–1.632)	63	–	1
Daejeon	55,168	1.466 (1.419–1.515)	40	–	3
Gwangju	52,469	1.481 (1.427–1.536)	34	–	3
Ulsan	41,242	1.556 (1.496–1.618)	37	–	6
Overall		**1.517 (1.461–1.574)**		**1.499 (1.354–1.658)**	
2 weeks before death					
Seoul	356,399	1.461 (1.444–1.479)	233	1.434 (1.382–1.488)	26
Busan	100,544	1.611 (1.564–1.659)	78	1.590 (1.491–1.695)	20
Incheon	91,384	1.469 (1.436–1.503)	72	–	7
Daegu	80,364	1.575 (1.527–1.625)	63	–	1
Daejeon	55,168	1.463 (1.414–1.514)	40	–	3
Gwangju	52,469	1.470 (1.416–1.527)	34	–	3
Ulsan	41,242	1.505 (1.453–1.559)	37	–	6
Overall		**1.506 (1.452–1.562)**		**1.497 (1.349–1.661)**	

Adjusted for sex, birth weight, gestational week, mother's age, mother's education level, season of birth.
No calculation of estimate due to small sample size (deaths < 10).

1.56–1.66) and the hazard ratios for every city were positive and statistically significant. Results for exposure during 2 weeks before death showed similar patterns with those of 1 month before death. Overall across the cities, we found statistically significant positive effects for total infant mortality for both exposure timeframes. For SIDS, we could estimate city-specific hazard ratios only for Seoul and Busan due to sample size. Analysis was based on a systematic exclusion criteria for sample size (> 10 death). City-specific hazard ratios for both cities and overall effect (for the two cities) were significantly positive for both exposure timeframes.

Table 4 shows overall effects across cities by infant's sex and maternal characteristics. We did not find evidence of effect modification across characteristics. For both exposure timeframes, hazard ratios for total infant mortality were slightly higher in female infants, infants born from younger (< 25 years) or older mothers (≥ 35 years), and infants from highly educated mothers (> 12 years). However, estimated effects were not statistically different between groups.

As sensitivity analysis, we compared the associations between heat exposure during 1 month before death and infant mortality with and without air pollution adjustment for PM_{10}. We did not adjust for ozone because ambient temperature was highly correlated with ozone (ranged from 0.74 to 0.89 by city) (see Table S2). After adjusting for PM_{10}, estimated effects for each city and overall effect were similar with original findings and were statistically significant (Table S3). We also compared the association using a variable for heat index instead of ambient temperature for Seoul. Results using a heat index were similar with original findings using an ambient temperature (Table S4). To account for long-term trend and seasonality, we adjusted for season of death in the model for the exposure during 1 month before death for which we observed significant associations. When considering season of death, the magnitude of hazard ratios for total infant mortality for various exposure metrics was similar compared with original findings and statistical significance remained although the magnitude of the hazard ratio for exposure during 1 month before death or 2 weeks before death reduced compared to those of the original findings (Table S5). We also conducted sensitivity analysis to account for temperature variation.

Table 4

Overall effects for a 1 °C increase in each exposure metric on total infant mortality across cities by characteristics.

Characteristics	1 month before death	2 weeks before death
Sex		
Male	1.518 (1.462–1.575)	1.514 (1.457–1.573)
Female	1.545 (1.459–1.636)	1.540 (1.452–1.632)
Mother's age (years)		
< 25	1.609 (1.355–1.909)	1.633 (1.342–1.987)
25–30	1.561 (1.495–1.630)	1.562 (1.503–1.622)
30–35	1.530 (1.442–1.625)	1.540 (1.435–1.652)
≥ 35	1.646 (1.370–1.978)	1.631 (1.300–2.047)
Mother's education (years)		
≤ 12	1.538 (1.439–1.644)	1.520 (1.425–1.621)
> 12	1.552 (1.484–1.623)	1.545 (1.487–1.605)

We adjusted for standard deviation of daily temperature in the model. When considering standard deviation of temperature, the magnitude of hazard ratios for total infant mortality for various exposure metrics did not vary greatly from the original analysis and statistical significance remained although the magnitude of the hazard ratio for exposure during 1 month before death or 2 weeks before death reduced compared to those of the original findings (Table S6).

4. Discussion

Overall across the seven cities, we found significantly positive association between ambient temperature during 1 month before death or 2 weeks before death and risk of infant mortality for total deaths or SIDS. The hazard ratios for total infant mortality for each city were all positive and statistically significant. We found suggestive evidence that some populations such as infants born from younger or older mothers may be more vulnerable to heat effect although we did not find statistical differences between groups.

Only a few previous studies have investigated the association between ambient temperature and mortality for infants. Our findings of positive association between ambient temperature and infant mortality are generally consistent with previous literature. A recent study by Basu et al. (2015) examined apparent temperature and all-cause or cause-specific infant mortality in California and reported excess risk for all categories of mortality except SIDS. Basu and Ostro (2008) identified subgroups vulnerable to high ambient temperature and found that higher mortality risk was especially pronounced for infants compared to other ages.

In this study we observed significant positive associations between ambient temperature during 1 month before death or 2 weeks before death and SIDS. SIDS is known to be one of major contributors for postneonatal mortality in several countries, however the possible risk factors for SIDS are not fully understood (Greenberg et al., 1973; Moon et al., 2007). Moreover, previous findings for the effect of ambient temperature on SIDS are not consistent. A recent study in Canada reported a strong association between elevated ambient temperature and risk of SIDS for infants 3–12 months of age (Auger et al., 2015). They suggested acute exposure to ambient heat may be an important risk factor for SIDS. Knöbel et al. (1995) examined the possible role of weather in SIDS in Taiwan and observed an association of climatic temperature with SIDS. Other studies found no association between SIDS and high ambient temperature or heat waves (Basu et al., 2015; Chang et al., 2013; Scheers-Masters et al., 2004). Previous literature suggests that several possible risk factors such as bedroom heating, sleeping position, overwrapping, and night sweating, which are linked with thermal stress, are associated with SIDS (Mitchell, 2009). Infants are more likely to be affected by heat exposure than older persons since the period of less than 1 year of age is a critical development period and less developed thermoregulatory systems may cause changes in blood flow and increased stress to critical organs (Guntheroth and Spiers, 2001; Xu et al., 2012).

Our study considered several exposure timeframes (e.g., whole gestation, each trimester, lifetime, and 1 month before death) to examine the critical exposure window for infant mortality in relation to heat. To date, little evidence on critical exposure windows exists on this health outcome and exposure. Most studies on the effect of ambient temperature and infant mortality examined short-term effects such as the effect of current day exposure or average exposures of a few previous days (Auger et al., 2015; Basu et al., 2015). To the best of our knowledge, there exists no earlier study to evaluate the relevant timeframe for heat exposure on infant mortality although some earlier studies did so for air pollution and infant mortality (Son et al., 2011; Woodruff et al., 2008). Thus, additional studies on biologically plausible exposure timeframes for infant mortality in relation to heat exposure are needed.

Previous studies reported several individual- and community-level effect modifiers of the temperature-mortality relationship across regions with different climate and population characteristics (Huang et al., 2015; Medina-Ramón et al., 2006; O'Neill et al., 2003). Our findings showed suggestive evidence that mother's age may be associated with the effect of high temperature on infant mortality. To summarize the existing overall evidence of effect modification of heat effect on infant health, we reviewed previous literature on adverse birth outcomes with heat exposure but different health outcomes since there is no previous study on effect modification of heat effect on infant mortality. Some studies suggested a higher susceptibility of some populations for heat effect on several birth outcomes. Basu et al. (2010) estimated the association between apparent temperature and risk of preterm delivery and observed greater association for infants of younger mothers. Another study in Rome also reported that infants of young mothers showed a higher susceptibility to temperature for preterm birth than those of older mothers (Schifano et al., 2013). A recent study reported greater effect of apparent temperature on the risk of stillbirth for male fetuses, and fetuses of younger mothers and less educated mothers (Basu et al., 2016). Another study investigating the association between high ambient temperature and risk of preterm delivery showed no significant differences by infant's sex or maternal education (Basu et al., 2010).

In this study, we found significant positive association between ambient temperature and infant mortality with similar effects across seven cities. The relationship between high temperature and health outcome or vulnerability to heat effect may vary spatially, and several studies demonstrated geographic variability, including within cities or between cities, in the impacts of high temperature on health outcomes or population's vulnerability to heat (Gasparrini et al., 2016). Several factors such as population characteristics (e.g., demographic, socioeconomic status), urbanization, and adaptation to climate may explain the variability of heat-related risk among different areas. A U.S. study found that mortality risk and key variables associated with spatial variability in heat-related risk vary by city (Hondula et al., 2015). In this region we did not find any evidence of heterogeneity in effects across cities, indicating that similar population characteristics and climates across cities may be possible explanations for our findings and thus similar policies can be applied across cities. Further study in other locations with different characteristics is needed to establish spatially targeted region-specific intervention and heat-related mitigation strategy.

This study has some limitations. Like most epidemiological studies, we used ambient temperature data from monitoring sites within each city rather than individual exposure for each study participant or spatially high resolution of temperature data, which may introduce exposure error. It is important to consider intra-urban spatial variability within the cities with respect to the association between ambient temperature and mortality. Also, different neighborhood characteristics including housing quality, poverty rate, land cover and land surface may partially explain the variability of heat-related mortality within the cities (Rosenthal et al., 2014; Xu et al., 2013). However, we could not consider high-resolution temperature data or neighborhood characteristics because those data were not available for this study, and we anticipate that potential bias from exposure misclassification is non-differential. Lee et al. (2016) compared the temperature-mortality association using a high spatial resolution temperature data from satellite images, and land use sources and monitoring station data. They found larger effect size for heat using high-resolution temperature data compared to results based on the sparser monitoring station data. Also, even if we have high spatial resolution of ambient temperature data within the city, the actual heat exposure for each study participants would relate with several factors such as activity patterns, amount of time spent indoors versus outdoors, and indoor temperature as well as use of adaptation measures (e.g., air conditioning). A previous study reported a positive association between ambient and body temperatures in the elderly that spent most time indoors in their homes (Basu and Samet, 2002b). We could not control for some potential confounding

factors for the relationship between temperature and infant mortality such as maternal risk factors (e.g., maternal smoking history, mother's previous medical condition). However, these factors may correlate with other variables such as maternal age and education level that were included in our models. Future study to consider the exposure data with more spatial variability or further information on potential confounding factors is needed.

To our knowledge, this is the first study to consider several exposure windows of heat exposure for infant mortality. This is also the first study to evaluate effect modification by sex and maternal characteristics in heat-related infant mortality in a multi-city study for Korea. Our findings provide evidence that heat exposure during 1 month before death or 2 weeks before death increases infant mortality from total deaths and SIDS in Korea. This evidence has implications for future studies evaluating health impacts of high temperatures or heat waves which could also impact health in infants and for policy makers to establish the strategies to reduce the risk of infant mortality from high ambient temperature under climate change.

Funding sources

Conflicts of interest

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.07.034.

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